Response of Thrombopoietin Receptor Agonists in MDM2 Inhibitor Induced Thrombocytopenia

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FPN: 674P

Background

- Inactivation of the p53 tumor suppressor pathway occurs mainly through mutations in TP53 (53% of tumors) or amplification of mouse double minute 2 (*MDM2)*, the gene which encodes for the oncoprotein MDM2
- MDM2 is an E3 ubiquitin ligase that targets p53 for proteasomal degradation and has been exploited as a therapeutic target
- Early phase trials have evaluated the efficacy and safety of MDM2 inhibitors, with thrombocytopenia being recognized as a class effect of these drugs
- Thrombopoietin Receptor Agonists (TPO-RAs) have been shown to improve thrombocytopenia secondary to chemotherapy
- It remains unknown if TPO-RAs improve thrombocytopenia induced by MDM2 inhibition

Methods

- Data was collected retrospectively for patients enrolled in any MDM2 inhibitor clinical trial from February 2014 to March 2023 at MSKCC
- *MDM2* amplification was detected by MSK-IMPACT or by central confirmation from respective study sponsors
- Patients were included if they were 18 years of age and received at least one dose of study medication
- Patients were excluded if they received a prior MDM2 inhibitor or had a history of a hematologic disorder/malignancy

Results

Table 1: Baseline characteristics of study population

Characteristic	N=113 (range/percent)
Median age	59 (19-89)
Gender	
Male	59 (52.2)
Female	54 (47.8)
Ethnicity	
White	95 (84.1)
Asian	12 (10.6)
Black/African American	4 (3.5)
Other/Unknown	2 (1.8)
Tumor type	
Liposarcoma	55 (48.7)
Other solid tumors (other sarcoma, melanoma, breast, colorectal, glioblastoma, salivary gland, ovarian, GEJ, anal, lung, prostate, urothelial, cholangiocarcinoma, testicular, NET)	58 (51.3)
MDM2 inhibitors	
Drug 1	43 (38.1)
Drug 2	42 (37.2)
Drug 3	17 (15.0)
Drug 4	11 (9.7)
Dosing schedules	
Once every 21 days	45 (39.8)
Daily x 21 days every 28 days	21 (18.6)
Days 1-3, 15-17 every 28 days	19 (16.8)
Days 1-7 every 21 days	11 (9.7)
Days 1-7 every 28 days	6 (5.3)
Days 1 and 8 every 28 days	6 (5.3)
Days 1-14 every 28 days	3 (2.7)
Once every 7 days	2 (1.8)
Median prior lines of therapy	2 (0-12)
Mean baseline platelet count (k/mcl)	262 (112-681)

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There are no COIs to disclose for the corresponding author

Figure 1: Study profile for patient inclusion

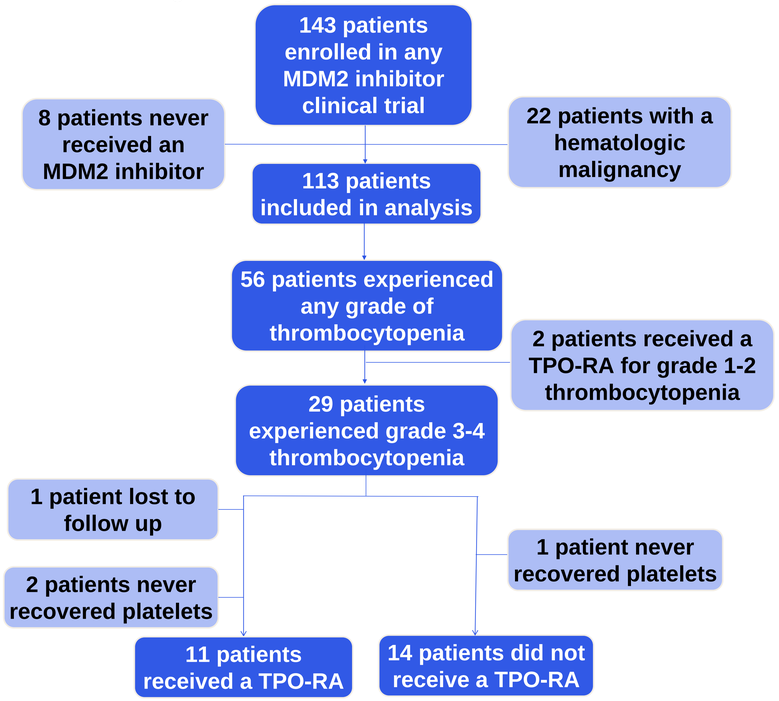


Figure 2: Median days to platelet recovery with 95% CI

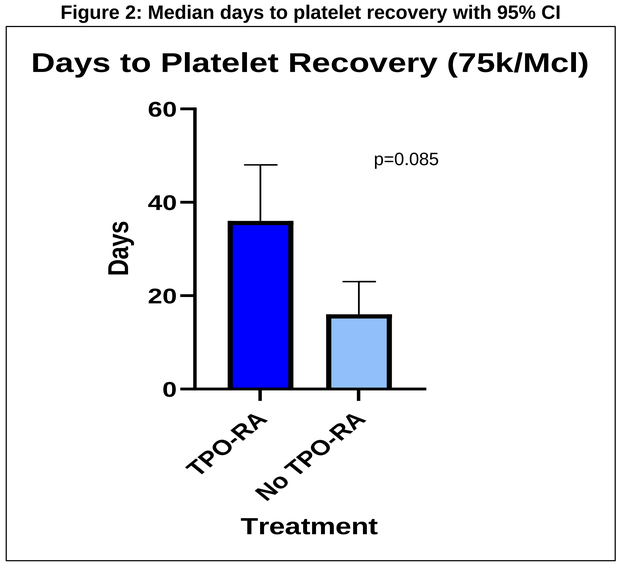
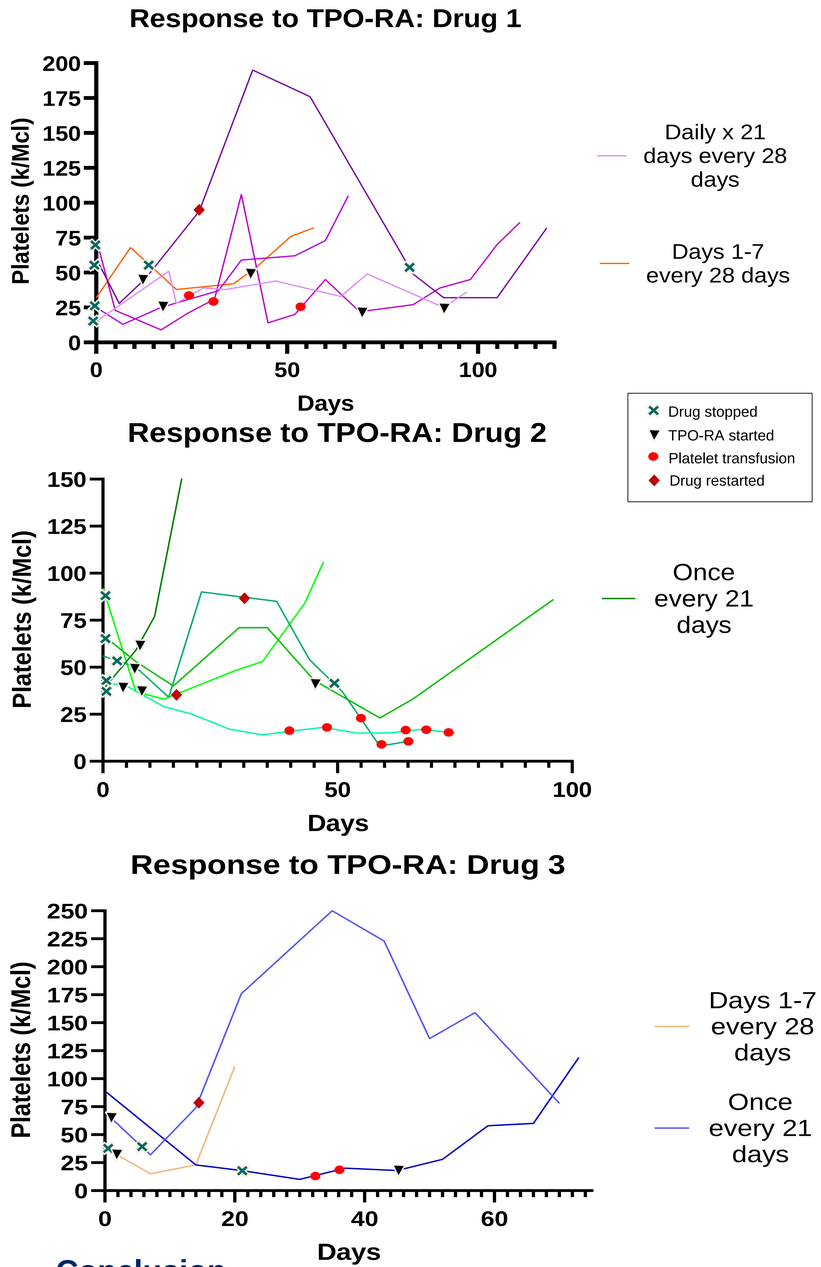


Table 2: Select safety outcomes for total population and TPO-RA/No-TPO-RA subgroups

Outcome	Total population N=113 (range/percent)	TPO-RA N=13 (range/percent)	No TPO-RA N=15 (range/percent)
Average time on treatment (months)	6.5 (0.20-42.9)	5.6 (1.5-12.4)	4.3 (0.70-13.5)
Dose interruptions	41 (36.3)	13 (100)	14 (93.3)
Dose reductions	31 (27.4)	6 (46.2)	7 (46.7)
Platelet transfusion	10 (8.8)	6 (46.2)	3 (20.0)
Major bleeding	0 (0)	0 (0)	0 (0)
Venous thromboembolism	3 (2.7)	0 (0)	0 (0)

Figure 3: Spaghetti plots for patients who received a TPO-RA (drugs 1-3) for MDM2 inhibitor induced thrombocytopenia



Conclusion

- There was no difference in days to resolution of MDM2 inhibitor induced grade 3-4 thrombocytopenia for patients who received a TPO-RA vs. patients who did not receive a TPO-RA
- There was no incidence of major bleeding or venous thromboembolism in the TPO-RA and No-TPO-RA cohorts
- This study is limited by heterogeneity of the patient population and concurrent treatment modalities for thrombocytopenia

References

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2. Soff GA, Miao Y, Bendheim G, et al. Romiplostim treatment of chemotherapy-induced thrombocytopenia. J Clin Oncol. 2019;37(31):2892-2898.